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EXAMINER

SOUAYA, JEHANNE E

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 03/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

BEST AVAILABLE COPY

Office Action Summary	Application No. 09/759,508	Applicant(s) Fishman
	Examiner Jehanne Souaya	Art Unit 1634
		
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
Period for Reply		
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> - Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). 		
Status		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Dec 9, 2002</u>		
2a) <input checked="" type="checkbox"/> This action is FINAL. 2b) <input type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
Disposition of Claims		
4) <input checked="" type="checkbox"/> Claim(s) <u>1-6 and 8-19</u> is/are pending in the application.		
4a) Of the above, claim(s) <u>8-19</u> is/are withdrawn from consideration.		
5) <input type="checkbox"/> Claim(s) _____ is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>1-6</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
Application Papers		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input checked="" type="checkbox"/> The drawing(s) filed on <u>Jan 12, 2001</u> is/are a) <input checked="" type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner.		
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner.		
If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
Priority under 35 U.S.C. §§ 119 and 120		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).		
a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of:		
1. <input type="checkbox"/> Certified copies of the priority documents have been received.		
2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.		
3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).		
*See the attached detailed Office action for a list of the certified copies not received.		
14) <input checked="" type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).		
a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
Attachment(s)		
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____		

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DETAILED ACTION

1. Currently, claims 1-6 and 8-19 are pending in the instant application. Claim 7 has been canceled, and claims 8-19 are withdrawn from consideration as being drawn to non elected inventions. Claims 1-6 are under consideration. All the amendments, arguments, and the declaration under 37 C.F.R. 1.131 have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied (necessitated by amendment) or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 1, 2, and 4 under 35 USC 102(b) as being anticipated by Jackel et al is moot in view of the amendment to claim 1 which states 'a titin related disease or condition *of the heart*'. Accordingly, the rejections of claim 3 under 35 USC 103 as being unpatentable over Jackel alone or in view of Satoh are moot.

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New Grounds of Rejection

Claim Rejections - 35 USC § 112

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary

Amount of Direction and Guidance

Presence and Absence of Working Examples

Nature of the Invention

Level of predictability and unpredictability in the art

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has or is at risk of developing *any* titin related disease or condition of the heart by detecting *any* mutation from a titin gene. The claims are further drawn to detecting heart failure.

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The specification teaches the claimed recitation of a “titin gene” is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebrafish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source (that is, any species), which have not been taught or described in the specification. The specification does not specifically define what is encompassed by “disease or condition *of the heart*”, therefore, such has been broadly interpreted to encompass any disease or condition of the heart including risk factors of heart failure outlined on page 1, lines 23-25. The specification defines “titin related disease or condition” to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Such a recitation encompasses any substitution, deletion or insertion in any titin gene. The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites “a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation” (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as

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to what is encompassed by the *pickwick* mutation. This recitation, therefore, has been broadly interpreted to encompass any mutation that is responsible for the *pickwick* phenotype (p. 19, lines 4-5). The specification, however, has only taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos. Such a teaching is insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in a weak heartbeat in zebrafish embryos or any other subject. The single point mutation taught in the specification also does not provide one of skill in the art with a predictable correlation between any mutation in any titin gene from any source and any disease or condition of the heart, including heart failure.

The specification lacks sufficient guidance to enable one of skill in the art to make or use the invention as broadly as it is claimed, without undue experimentation. To practice the invention as broadly as it is claimed the skilled artisan would have to perform a large study which included subjects affected with a large number of different diseases or conditions of the heart as well as controls and to screen such for any mutation in a titin gene. Such analysis would consist of trial and error research projects, the results of which are unpredictable. It is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. The effects of these changes, however, are largely unpredictable as to which ones have a significant effect versus not. The specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the

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titin protein. Without such, the skilled artisan would further be unable to predictably correlate which mutations would have and would not have an effect on the function or activity of any titin protein.

The art exemplifies such unpredictability with regard to titin mutations as Itoh-Satoh et al (Biochemical and Biophysical Research Communications, vol. 291, pp 385-393; 2002) teach a mutation in the titin gene which may be associated with Dilated Cardiomyopathy (p. 387, col. 2, lines 7-13), another mutation, Arg328Cys, was found in healthy control subjects, indicating that it is a polymorphism not related with DCM (col. 2, lines 3-5).

Therefore, based on the lack of guidance provided in the specification and the unpredictability taught in the art with regard to an association between a specific mutation in a titin gene and protein and any disease or condition of the heart, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it claimed. The skilled artisan would not only be required to screen for a large number of mutations, but would also have to determine whether a statistically significant correlation was present between each mutation and a specific disease or condition of the heart. Such would require trial and error analysis, the results of which are unpredictable as exemplified by the teachings of Itoh-Satoh.

Response to Arguments

The response traverses the rejection. The response asserts that the amendment to claim 1 to specify a “naturally occurring titin gene” overcomes the examiner’s basis for rejection

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regarding the definition of “titin gene” given in the specification. The amendment and argument have been thoroughly reviewed but were not found persuasive. The term “naturally occurring titin gene” encompasses titin genes from any species. In the previous office action, the examiner stated that the term “titin gene” as defined by the specification, encompasses mutants, allelic variants, and homologs of titin from any source. “Any source” includes any species, which is still an extremely large number of possible allelic variants, mutants, and homologs of any titin gene, which is encompassed by the amended claims and does not narrow the scope of the claims sufficiently to overcome the rejection.

The response asserts that the amendment to claim 1 to specify a ‘titin related disease or condition *of the heart*’ overcomes the basis for the rejection with regard to the examiner’s statement that ‘the only mutation described in the specification is one that was found in zebrafish embryos with a weak heart beat’. This amendment and argument have been thoroughly reviewed but were found unpersuasive as such a recitation still encompasses a large number of diseases. The previous office action stated that the teachings of the specification, that is the single mutation taught, does not provide one of skill in the art with a predictable correlation between any mutation in any titin gene from any source and any disease or condition, “including heart failure” (see sentence bridging pages 4 and 5 of the previous action). Therefore, the amendment of the claims to specify a disease or condition of the heart still encompasses a large number of possible mutations in any titin gene, allelic variant, or homolog, wherein the specification has not provided a predictable correlation between such mutations and the large number of possible

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diseases or conditions of the heart, including heart failure. As stated in the previous office action, the art teaches the unpredictability of associating any mutation in a titin gene and any disease or condition of the heart. Itoh-Satoh et al (Biochemical and Biophysical Research Communications, vol. 291, pp 385-393; 2002) teach a mutation in the titin gene (which leads to a mutated titin protein), Arg328Cys, was found in healthy control subjects, indicating that it is a polymorphism not related with dilated cardiomyopathy (col. 2, lines 3-5) (considered a disease or condition of the heart). Therefore, although the claims have been narrowed to specify a disease or condition of the heart, the specification does not enable the full scope of the claimed invention to overcome the unpredictability taught in the art with regard to the association of any mutation in any titin gene from any source and any disease or condition of the heart. The response further asserts that the amendment of the claims to specify a disease or condition of the heart also overcomes the basis for the rejection concerning the single mutation taught in the specification which is associated with a weak heartbeat in zebrafish. This argument has been thoroughly reviewed but was found unpersuasive. While, the specification has taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos, such a teaching is insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in a weak heartbeat in zebrafish embryos or any other subject, let alone any disease or condition of the heart, including heart failure. Firstly, as stated above, the claims still encompass any mutation in any titin gene, which are not necessarily predictably correlated to any disease or

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condition of the heart as exemplified by the teachings of Itoh-Satoh. Secondly, the recitation of “disease or condition of the heart” encompasses a large number of diseases or conditions which are not necessarily a result of a weak heartbeat. For example, although the phenotype of the zebrafish, that is a weak heartbeat, may be similar to mammalian heart failure, such is not necessarily diagnostic of mammalian heart failure, let alone any disease or condition of the heart. In other words, while a weak heart beat may lead to heart failure, there are other causes for heart failure including coronary artery disease, hypertension and diabetes (as taught by the specification at page 1). Therefore, while coronary artery disease, hypertension, or diabetes may all lead to heart failure, a mutation which is associated with any one of such risk factors is not necessarily *diagnostic* of another. Each risk factor represents specific diseases which have different causes in and of themselves. As noted in the previous office action, it is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. The effects of these changes, however, are unpredictable as to which ones have a significant effect versus not, as exemplified by the teachings of Itoh-Satoh. The specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the titin protein, such that the skilled artisan would be able to predictably correlate which mutations would have an effect on the function or activity of any titin protein and therefore be able to determine which mutations would be predictably diagnostic of any specific disease or condition of the heart, including heart failure.

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The response further asserts that the analysis of the sequences of titin genes from patients and the correlation of any detected mutations with a disease or condition of the heart would not require undue experimentation as is shown by the teachings of Satoh (cited in the 102(a) rejection) and that the experiments of Itoh-Satoh do not negate the fact that detection of mutations in the titin gene can be correlated with diseases or conditions of the heart without undue experimentation. This argument has been thoroughly reviewed but was found unpersuasive. The previous office action did not dispute the fact that *specific* mutations in the human titin gene exist which are associated with *specific* diseases or conditions of the heart. However, the full scope of the claimed invention is much broader, such that the single mutation in zebrafish taught in the specification does not establish a predictable correlation that *any* mutation in *any* titin gene, variant, or homolog, is associated with *any* disease or condition of the heart, including heart failure, to overcome the unpredictability taught in the art with regard to titin mutations and heart disease. Case law has established that “(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that “(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art”. The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. The teachings of Itoh-Satoh exemplify that associating any mutation in the titin gene

with any disease or condition of the heart is unpredictable (Itoh-Satoh teaches that a mutation exists in the titin gene which results in an altered titin protein sequence and that such is not associated with dilated cardiomyopathy, a disease or condition of the heart). Therefore, given that the specification has only taught a single mutation in a zebrafish titin gene and has not correlated how this mutation would be associated with any disease or condition of the heart, such as hypertension or coronary artery disease, in any titin gene, variant or homolog, the specification does not enable the full scope of the claimed invention. To practice the invention as broadly as it is claimed, the skilled artisan would have to perform trial and error analysis to determine which of the large number of possible mutations in any titin gene is associated with any specific disease or condition of the heart, including heart failure. As Itoh-Satoh exemplifies that such analysis is unpredictable as to which mutations have a significant effect versus not, such analysis is considered undue.

Written Description

6. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for determining whether a test subject from any source, including mammals and humans, has or is at risk of developing *any* titin related

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disease or condition of the heart by detecting *any* mutation in a naturally occurring titin gene.

The claims are further drawn to detecting heart failure.

The specification teaches that claimed recitation of a “titin gene” is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebrafish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The disclosure of the single human titin gene and polypeptide in the specification, however, is not representative of the large number of mutants, variants and homologues encompassed by the claimed invention. The specification does not specifically define what is encompassed by “disease or condition *of the heart*”, therefore, such has been broadly interpreted to encompass any disease or condition of the heart including risk factors of heart failure outlined on page 1, lines 23-25. The specification defines “titin related disease or condition” to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Such a recitation encompasses any substitution, deletion or insertion in any titin gene. The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). Such a teaching is not representative of the large number of substitutions, deletions, and insertions in any naturally occurring titin gene from any source that are encompassed by the claimed invention. Further, the single mutation taught is not representative of the large number

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of mutations that could be responsible for the *pickwick* phenotype. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. The specification has only taught a single mutation that appears to be associated with a weak heart beat in zebrafish embryos. The specification provides insufficient written description to support the genus of titin genes or mutations encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims

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directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Accordingly, absent a teaching of a representative number of titin nucleic acids and mutations, the specification does not provide a written description of the invention of claims 1-6.

Response to Arguments

The response traverses the rejection. The response asserts that the amendment to claim 1 to specify a "naturally occurring titin gene" overcomes the examiner's basis for rejection regarding the definition of "titin gene" given in the specification. This amendment and argument have been thoroughly reviewed but was not found persuasive. The term "naturally occurring titin gene" encompasses titin genes from any species. In the previous office action, the examiner stated that the term "titin gene" as defined by the specification, encompasses mutants, allelic variants, and homologs of titin from any source. "Any source" includes any species, which is still an extremely large number of possible allelic variants, mutants, and homologs of any titin

gene, which is encompassed by the amended claims and does not narrow the scope of the claims sufficiently to overcome the rejection.

The response also asserts that the present claims are drawn to methods of diagnosing diseases or conditions of the heart by detection of mutations in titin genes and not to mutant titin genes themselves. The response further asserts that the statements regarding that the nucleic acid is required is more appropriate in a rejection of claims to nucleic acids or proteins and not to methods that involve the detection of mutations. These arguments have been thoroughly reviewed but were found unpersuasive. The basis for the rejection made in the previous office action is with regard to the large genus of undisclosed diagnostic mutations in the large number of undisclosed titin genes, variants, and homologs from any species encompassed by the claims. In this case, the methods are not only drawn to detecting mutations in a specific gene, they are drawn to and encompass *determining whether any subject has or is at risk of developing* a titin related disease or condition of the heart by detecting mutations in *any* titin gene, variant, or homolog. The specification has only taught a single titin nucleic acid (human) and the mutation characteristic of a weak heartbeat in zebrafish taught in the specification is not in the human sequence provided, but the titin gene of a zebrafish. This single mutation is not representative of the large genus of possible diagnostic mutations of any titin related disease or condition of the heart, in the large number of undisclosed titin genes, variants, and homologs in any species which are encompassed by the claimed methods.

The response further asserts that methods of diagnosing diseases or conditions of the heart by detection of mutations in titin gene are adequately described in the specification, which describes obtaining samples from patients and analysis of titin sequences, and that it is not necessary for the specification to list every possible mutation that could be associated with these diseases or conditions as they can be easily identified by comparison with sequences from healthy controls. These arguments have been thoroughly reviewed but were not found persuasive. While the specification provides general description of how to detect mutations in known sequences, the *claims* are drawn to detecting a large number of possible undescribed diagnostic mutations (for any disease or condition of the heart) in a large number of undisclosed and undescribed titin genes, variants, and homologs, in any species. The rejection in the previous office action did not require that every possible mutation that could be associated with these diseases, or that every possible titin sequence, be identified or disclosed. Rather, the rejection stated that “[the mutation taught in the specification] is not representative of the large number of substitutions, deletions, and insertions in any [naturally occurring] titin gene from any source that are encompassed by the claimed invention.” With regard to specific mutations, the specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebrafish embryos characterized with a weak heartbeat (see p. 20). The whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon, however the specific leucine residue where this mutation occurs, is not

taught. This single mutation is not representative of the extremely large genus of possible undisclosed diagnostic mutations (of any disease or condition of the heart), in the large number of undisclosed titin genes, variants, and homologs from any species which are encompassed by the claimed methods.

Maintained Rejections

Claim Rejections - 35 USC § 102

7. Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Satoh et al (Biochemical and Biophysical Research Communications, vol. 262, pp 411-417, 1999).

With regard to claims 1 and 4-6, Satoh teaches of an A to T transversion in codon 740 of the titin gene of a patient with hypertrophic cardiomyopathy, which replaces an Arginine with Leucine (see abstract). Satoh teaches that this mutation was not found in more than 500 normal chromosomes (see abstract). With regard to claims 2 and 3, Satoh teaches that genomic DNA was extracted from each subject and that PCR primers flanking each exon of the titin gene were designed to amplify each exon (p. 412-col. 1, “PCR-DCP analysis”) and that to identify the mutation in exon 14, the PCR product was cloned into a vector and sequenced (para. bridging cols 1 and 2, p. 412).

Response to 37 CFR 1.131 Declaration

8. The declaration filed on December 9, 2002 under 37 CFR 1.131 has been thoroughly considered but is ineffective to overcome the reference. The following deficiencies were found:

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A) The declaration does not contain an allegation that the acts relied upon to establish the date prior to the reference were carried out in this country or in a NAFTA country or WTO member country (see MPEP 715.07(c)).

B) The declaration is only executed by one inventor, however it is unclear whether both inventors invented the subject matter in claims 1-6 or which inventor invented the subject matter in each claim (for example, paragraph 2 of the declaration states “my co-inventor and I”) MPEP 715.04 states:

WHO MAY MAKE AFFIDAVIT OR DECLARATION

The following parties may make an affidavit or declaration under 37 CFR 1.131:

(A) *All the inventors of the subject matter claimed.*

(B) *An affidavit or declaration by less than all named inventors of an application is accepted where it is shown that less than all named inventors of an application invented the subject matter of the claim or claims under rejection. For example, one of two joint inventors is accepted where it is shown that one of the joint inventors is the sole inventor of the claim or claims under rejection...*

Affidavits or declarations to overcome a rejection of a claim or claims must be made by the inventor or inventors of the subject matter of the rejected claim(s), a party qualified under 37 CFR 1.42, 1.43, or 1.47, or the assignee or other party in interest when it is not possible to produce the affidavit or declaration of the inventor(s). Thus, where all of the named inventors of a pending application are not inventors of every claim of the application, any affidavit under 37 CFR 1.131 could be signed by only the inventor(s) of the subject matter of the rejected claims. Further, where it is shown that a joint inventor is deceased, refuses to sign, or is otherwise unavailable, the signatures of the remaining joint inventors are sufficient. However, the affidavit or declaration, even though signed by fewer than all the joint inventors, must show completion of the invention by all of the joint inventors of the subject matter of the claim(s) under rejection. In re Carlson, 79 F.2d 900, 27 USPQ 400 (CCPA 1935).

C) The declaration and the exhibit have been thoroughly reviewed but are not sufficient to overcome the rejection. Firstly, it is noted that the exhibit was difficult to read and follow in places and that an explanation of relevant steps was not provided in the declaration. However, combined with the statements in the declaration [that the exhibit shows that the pickwick mutation, which is characterized by a weak heart beat is in the titin gene and that in particular

certain zebrafish sequences identified as being in the pickwick locus were homologous to known titin sequences], the exhibit and declaration would be sufficient to overcome the reference with regard to claims 1-3 (provided that the deficiencies outlined above are corrected). With regard to claims 4-6, neither the statement in the declaration (para 2) nor the exhibit exemplify actual or constructive, conception or reduction to practice, of 1) a method to determine whether a *mammal or a human* (claims 4 and 5) is at risk of developing a titin related disease or condition of the heart by determining whether a *mammal or a human* has a mutation in a naturally occurring titin gene or 2) a method for determining whether a test subject has titin related *heart failure* (claim 6), before the August 1999 publication date of the Satoh reference. The exhibit has been thoroughly reviewed and seems to provide evidence that the pickwick mutation in the zebrafish could be titin (p. 004) and that “Y5T7 end is titin homologue” (p. 005). While the provisional application 60/175,787 shows constructive conception and reduction to practice of the invention of claims 4-6, conception or reduction to practice for the invention of claims 4-6 could not be determined from the exhibit or the declaration.

For these reasons, the rejection of claims 1-6 under 35 USC 102(a) as being anticipated by Satoh et al, is maintained.

Inventorship

9. In view of the papers filed December 9, 2002, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the

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inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding inventor Xiaolei Xu such that the correct inventorship of the instant application is Mark C. Fishman and Xiaolei Xu.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya

Patent examiner

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2/20/03